RESEARCH ARTICLE

Factors predicting neuronal surface antibodies in the elderly with new-onset and unknown seizures

Xiao Liu[1,2], Tingting Yu[1,2], Jing Qi[1,2], Ruijuan Lv[1,2] & Qun Wang[1,2,3] iD

[1]Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China
[2]China National Clinical Research Center for Neurological Diseases, Beijing, China
[3]Beijing Institute of Brain Disorders, Collaborative Innovation Center for Brain Disorders, Capital Medical University, Beijing, China

Correspondence
Qun Wang, Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China. Tel: +86-10-59978544; Fax:+86-10-59978544; E-mail: wangq@ccmu.edu.cn

Abstract

Objective: To investigate risk factors of neuronal surface antibodies (NSAbs) and develop a nomogram that could identify patients at the odds of NSAbs among the elderly (aged 60 years or older) with new-onset seizures of unknown etiology. **Methods:** Clinical data for aged ≥60 years diagnosed with new-onset seizures of unknown etiology were retrospectively reviewed. A nomogram based on multivariable logistic regression was constructed. Model performance of nomogram was evaluated using area under the curve (AUC), calibration curve, decision curve analysis (DCA), and clinical impact curve (CIC). Meanwhile, it was internally validated by bootstrap validation in current cohort. **Results:** Of 147 patients included in final analysis, 68 (46.3%) had NSAbs-mediated encephalitis. Six factors were identified: duration of seizures less than 3 months (OR:14.259; 95% CI: 4.480–45.386), focal-onset seizures (OR:12.457; 95% CI: 2.710–57.261), psychiatric deficits (OR:10.063; 95% CI: 3.231–31.343), sleep disorders (OR:3.091; 95% CI: 1.011–9.454), hyponatremia (OR:6.252; 95% CI: 1.445–27.043), and medial temporal lobe (MTL) lesions on MRI (OR:4.102; 95% CI: 1.382–12.169). The nomogram had a good discrimination with an AUC of 0.916 and with a corrected AUC of 0.881 after the bootstrapping validation, our model also exhibited a better predictive performance than scoring systems commonly used clinically. Additionally, the calibration curve showed that predicted NSAbs-positive rates of nomogram were closely aligned with actual observed results. Moreover, the nomogram achieved well on clinical utility by using the DCA and CIC. **Interpretation**: Our nomogram may provide a convenient and useful tool for identifying the elderly with new-onset seizures of unknown etiology who are at risk of NSAbs-mediated encephalitis, which would allow these patients receive earlier immunotherapy.

Introduction

Epilepsy in the elderly is a common brain condition and has higher disability or mortality compared with younger populations.[1] Prior studies showed cerebrovascular disease and dementia were the most prominently recognized etiologies in older patients with new-onset and symptomatic seizures or epilepsy and approximately 13%–52.8% were with an unknown etiology.[1–3] Although many studies have shown that seizures or epilepsy are common in patients with antibody-mediated encephalitis since the neuronal surface antibodies (NSAbs) emerged in 2007,[4–6]

the NSAbs-mediated encephalitis is a rare and easily neglected cause of seizures in the elderly. Thus, it is necessary that the identification of autoimmune etiology for previously new-onset seizures of unknown etiology in the older patients.[7,8]

However, the term of "autoimmune epilepsy" has been challenged because many patients with the NSAbs-mediated encephalitis could experience complete seizure freedoms and ultimately terminate anti-seizure medications (ASMs) in the acute phase of disease.[9,10] Certainly, a minority of patients (10%–28%) may eventually develop chronic epilepsy due to an enduring predisposition to

unprovoked seizures.[11,12] To clarify the relationship between seizures or epilepsy and autoimmune encephalitis, the terms of "acute symptomatic seizures (ASS) secondary to autoimmune encephalitis" and "autoimmune-associated epilepsy (AAE)" were proposed by International League Against Epilepsy (ILAE) in 2020,[13] which was highly important to early differentiate ASS from epilepsy because the former mainly respond better to immunotherapy rather than anti-seizure medications.[14] In addition, the early identification and intervention of autoimmune etiology in patients with ASS may avoid the formation of chronic epilepsy and long-term application of ASMs.[15,16] Therefore, identifying clinical variables to predict antibody-mediated encephalitis is of critical importance to improve clinical prognosis in patients with new-onset and symptomatic seizures. The previous studies have suggested that some scoring systems [antibody prevalence in epilepsy (APE) score, APE^2 score, APE^2-China (CHN) score] could be used to determine the neurological autoantibodies among patients with seizures and epilepsy of unknown etiology.[17–20] Another studies also evaluated clinical features which predict neuronal antibodies in adult patients with new-onset focal epilepsy.[21,22] Nevertheless, on the one hand, prior studies mainly focused on the adults and lacked specifically relevant research on the older patients; on the other hand, these studies purely relied on serological data rather than combining serological and cerebrospinal fluid (CSF) data, which might lead to missed NSAbs-positive cases.[23]

Therefore, we retrospectively identified patients ≥60 years of age with new-onset and symptomatic seizures of unknown etiology, and aimed to determine which clinical factors could affect the presence of antibodies against neuronal surface antigens in serum and CSF, and subsequently develop a nomogram that could identify patients at risk of NSAbs among the elderly with new-onset and symptomatic seizures of unknown etiology.

Methods

Study design and participants

This study was conducted in accordance with principles of the Declaration of Helsinki. Ethics approval was obtained from the Ethics committee of Beijing Tiantan hospital, Capital Medical University, Beijing, China. All patients provided informed consent for the use of their medical records.

In this retrospective study, we included inpatients with the elderly (≥60 years old) diagnosed with new-onset seizures between 01 Jan 2015, and 31 Dec 2021, at the Department of Neurology, Beijing tiantan hospital, Capital Medical University. The enrollment criteria were as follows: (1) age 60 years or older; (2) all included patients presented with seizures or epilepsy, which was diagnosed with clinical characteristics of seizures and electroencephalogram (EEG), and first seizure occurred after the age of 60 years; (3) Neuronal antibodies detections were performed in serum and CSF. The exclusion criteria were as follows: (1) new-onset seizures with definite etiology, including stroke, brain trauma, brain tumors, metabolic diseases, and others; (3) the baseline information missed. The eligible patients in the final analysis were further classified as NSAbs-positive and NSAbs-negative groups according to results of antibodies detections.
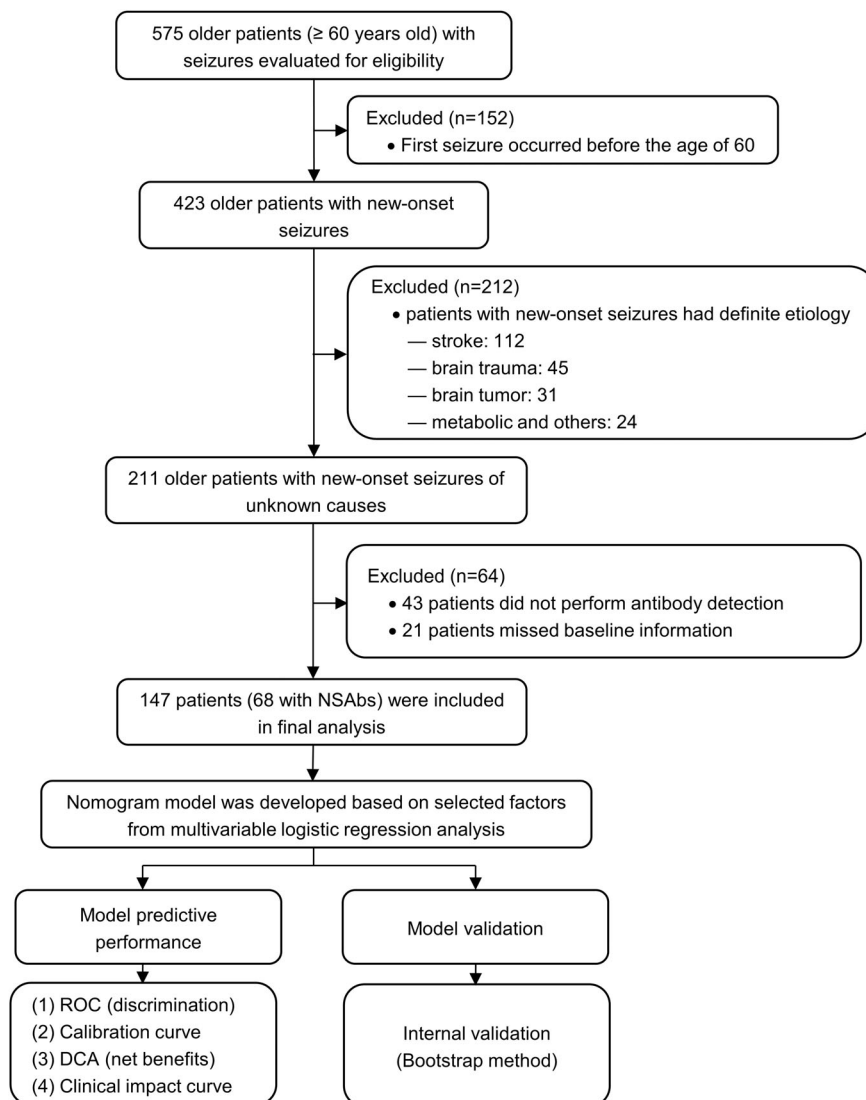
Antibody detection

The serum and CSF samples were simultaneously sent to the neuroimmunology laboratory of the Peking Union Medical College Hospital (Beijing, China) for screening NSAbs using both cell-based assays (CBA, Euroimmun, Lübeck, Germany) and immunohistochemical analysis. The covered NSAbs included N-methyl-D-aspartate receptor (NMDAR), leucine-rich glioma-inactivated 1 (LGI1), contactin-associated protein-2 (CASPR2), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), and γ-aminobutyric acid type B (GABAB).

Data collection and definition

All data collection was carried out using standardized forms and protocols from electronic medical records, and the data were carefully checked for reliability and consistency. (1) Demographics: age and sex. (2) Medical history: smoking, drinking, hypertension, and diabetes. (3) Seizure features: seizure duration, types of seizure onset, seizure frequency, and status epilepticus. Seizure duration was divided into two categories according to the 3 months' period, the duration of seizures less than 3 months was defined as "the time interval from seizure onset to hospitalized admission was less than 3 months". Types of seizure onset was categorized as focal, generalized, and unknown onset (details see operational classification of seizure types proposed by ILAE 2017),[24] It needed to be emphasized that faciobrachial dystonic seizures (FBDS) were considered a special form of focal-onset seizures in current study. Seizure frequency was obtained by searching medical records at admission prior to initiation of treatment, and then categorized as daily seizure or not (daily seizure was defined as ≥1 seizure per day). (4) Comorbid symptoms: Cognitive impairment (including memory, executive function, disorientation, and activity of daily living). Psychiatric deficits (including anxiety, depression, mood change, personality change, abnormal behaviors, and hallucination). Sleep disorders (including insomnia, hypersomnolence, rapid eye movement sleep behavior

Figure 1. Flow diagram of study design and participants. NSAbs, neuronal surface antibodies; ROC, receiver operating curve; DCA, decision curve analysis.

575 older patients (≥ 60 years old) with seizures evaluated for eligibility

Excluded (n=152)
• First seizure occurred before the age of 60

423 older patients with new-onset seizures

Excluded (n=212)
• patients with new-onset seizures had definite etiology
— stroke: 112
— brain trauma: 45
— brain tumor: 31
— metabolic and others: 24

211 older patients with new-onset seizures of unknown causes

Excluded (n=64)
• 43 patients did not perform antibody detection
• 21 patients missed baseline information

147 patients (68 with NSAbs) were included in final analysis

Nomogram model was developed based on selected factors from multivariable logistic regression analysis

Model predictive performance

(1) ROC (discrimination)
(2) Calibration curve
(3) DCA (net benefits)
(4) Clinical impact curve

Model validation

Internal validation
(Bootstrap method)

disorder, and sleep apnea, periodic limb movements). Speech problems (including aphasia and dysarthria). Autonomic dysfunction (including blood pressure, heart rate, perspiration, weight, bowel and bladder dysfunction). (5) Accompanied tumors: Tumor screening was performed at admission by clinical, laboratory and imaging examinations, and the definite diagnosis was based on the pathological diagnosis after surgery. (6) Laboratory examinations: CSF pleocytosis was defined as leukocyte count of >5/μl. Elevated CSF protein levels was defined as >45 mg/dl. Positive oligoclonal bands was defined that oligoclonal bands were detected by serum and CSF immunofixation electrophoresis. Serum sodium values were collected at admission, and hyponatremia was defined as $Na^+ < 135$ mmol/L. Serum homocysteine was also included in this study. (7) EEG patterns: mainly including temporal slow waves or epileptiform discharges; (8) Neuroimaging findings: medial temporal lobe

(MTL) hyperintensity on fluid attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI), which implied inflammatory edema within the hippocampus and amygdala in the acute stage of limbic encephalitis. (9) Treatments: ASMs were collected by searching medical records. Immunotherapy included intravenous methylprednisolone, intravenous immunoglobulins, rituximab, and mycophenolate mofetil. (10) Prior scoring systems for autoimmune seizures and epilepsy: APE, APE[2], and APE[2]-CHN scores were calculated for each patient who participated this study.

Statistical analysis

Statistical analysis was carried out using *SPSS* 26.0 software package (IBM Corp., Armonk, NY) and *R*-4.1.2 (*R* Development Core Team, Vienna, Austria) for Windows. First, the normal distribution of data were tested by the

Table 1. Baseline clinical characteristics between patients with and without NSAbs.

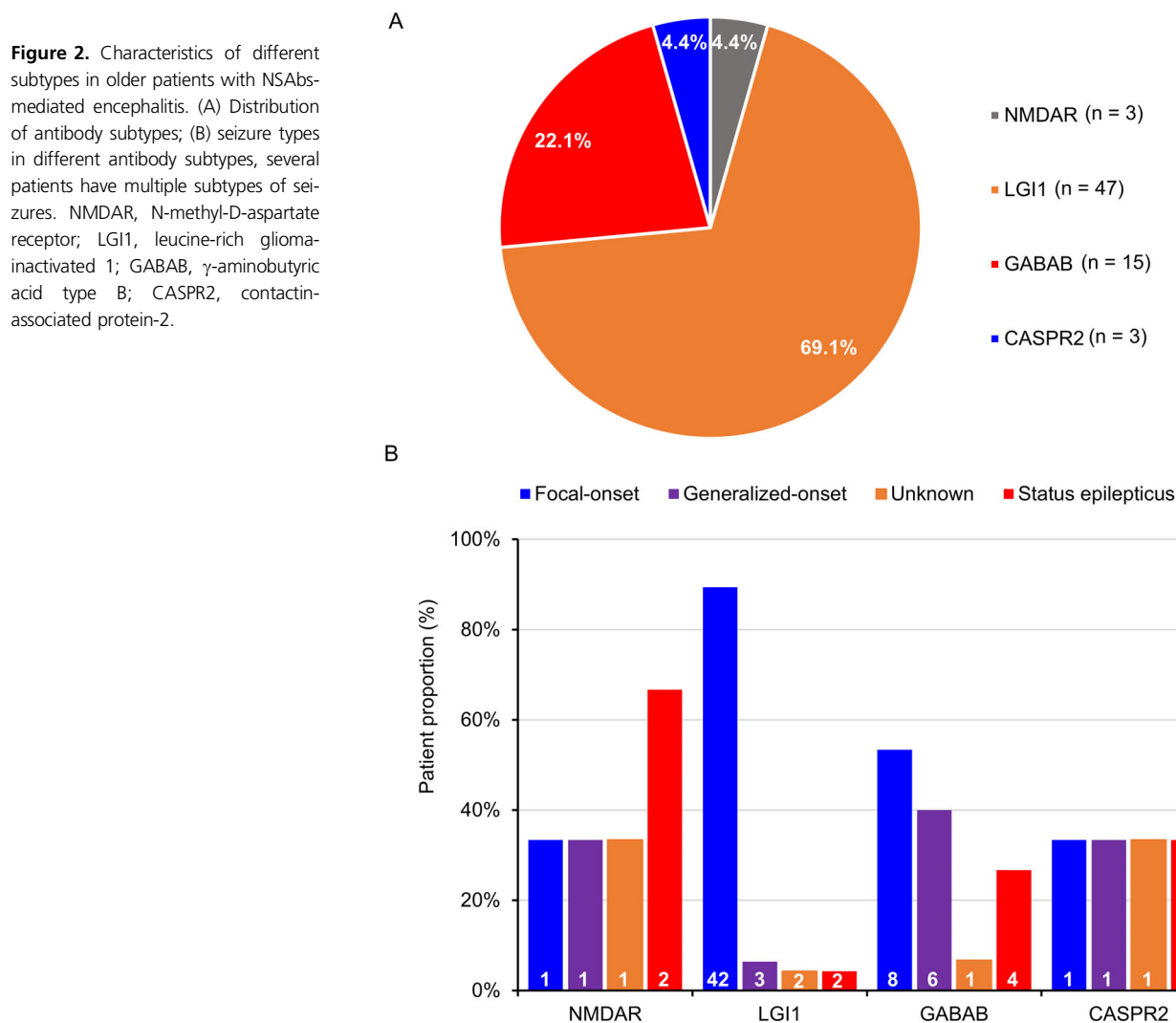| Clinical characteristics	Overall (n = 147)	NSAbs-positive group (n = 68)	NSAbs-negative group (n = 79)	p value
Male, n (%)	107 (72.8)	48 (70.6)	59 (74.7)	0.578
Age at onset, n (%)				0.560
Young old (60 ≤ age<70)	106 (72.1)	49 (72.1)	57 (72.2)	
Middle old (70 ≤ age<80)	37 (25.2)	16 (23.5)	21 (26.6)	
Oldest old (80 ≤ age)	4 (2.7)	3 (4.4)	1 (1.3)	
Medical history, n (%)				
Smoking	55 (37.4)	27 (39.7)	28 (35.4)	0.594
Drinking	44 (29.9)	17 (25.0)	27 (34.2)	0.226
Hypertension	71 (48.3)	29 (42.6)	42 (53.2)	0.203
Diabetes	24 (16.3)	11 (16.2)	13 (16.5)	0.964
Duration of seizures less than 3 months, n (%)	66 (44.9)	45 (66.2)	21 (26.6)	<0.001
Seizure types, n (%)				0.005
Focal-onset	96 (65.3)	52 (76.5)	44 (55.7)	
Generalized-onset	24 (16.3)	11 (16.2)	13 (16.5)	
Unknown	27 (18.4)	5 (7.4)	22 (27.8)	
Seizure frequency (Daily seizures), n (%)	68 (46.3)	39 (57.4)	29 (36.7)	0.012
Status epilepticus, n (%)	20 (13.6)	9 (13.2)	11 (13.9)	0.903
Comorbid symptoms, n (%)				
Seizures only	37 (25.2)	7 (10.3)	30 (38.0)	<0.001
Cognitive impairment	95 (64.6)	53 (77.9)	42 (53.2)	0.002
Psychiatric deficits	68 (46.3)	47 (69.1)	21 (26.6)	<0.001
Sleep disorders	49 (33.3)	38 (55.9)	11 (13.9)	<0.001
Speech problems	5 (3.4)	4 (5.9)	1 (1.3)	0.182
Autonomic dysfunction	12 (8.2)	11 (16.2)	1 (1.3)	0.001
Accompanied tumors, n (%)	23 (15.6)	12 (17.6)	11 (13.9)	0.536
CSF abnormalities, n (%)				
Pleocytosis	37 (25.2)	24 (35.3)	13 (16.5)	0.009
Elevated protein levels	53 (36.1)	26 (38.2)	27 (34.2)	0.609
Positive oligoclonal bands	36 (24.5)	28 (41.2)	8 (10.1)	<0.001
Homocysteine, median (IQR), μmol/L	13.5 (5.5)	13.1 (6.0)	13.7 (4.8)	0.205
Hyponatremia, n (%)	33 (22.4)	28 (41.2)	5 (6.3)	<0.001
EEG abnormalities at onset, n (%)				
Temporal slow waves or epileptiform discharges	118 (80.3)	51 (75.0)	67 (84.8)	0.136
MTL lesions on MRI, n (%)	44 (29.9)	27 (39.7)	17 (21.5)	0.016
Treatments, n (%)				
Numbers of anti-seizure medications				0.137
0	6 (4.1)	5 (7.4)	1 (1.3)	
1	101 (68.7)	43 (63.2)	58 (73.4)	
≥2	40 (27.2)	20 (29.4)	20 (25.3)	
Immunotherapy	68 (46.3)	68 (100)	NA	NA

Abbreviations: NSAbs, neuronal surface antibodies, CSF, cerebrospinal fluid; IQR, interquartile range; EEG, electroencephalogram; MTL, medial temporal lobe; MRI, magnetic resonance imaging; NA, not applicable.

Shapiro–Wilk test. Continuous variables with a normal distribution were expressed as mean and standard deviations, and non-normal continuous variables are presented as the median (interquartile range, IQR). Continuous variables were compared using the *t*-test or nonparametric Mann–Whitney *U* test. Categorical variables were expressed as numbers with percentages (%) and evaluated using Chi-squared test or Fisher's exact test.

The risk factors associated with NSAbs-mediated encephalitis in older patients with new-onset seizures of unknown etiology were explored by a forward-stepwise multivariable logistic regression analysis. First, the significance of each variable was selected using univariable analysis for assessing possibly independent factors for the presence of NSAbs. The clinically relevant variables with $p < 0.1$ in the univariable analysis were included into the multivariable logistic regression model, to identify risk factors for positive NSAbs, and odds ratios (ORs) were reported with 95% CIs. A two-tailed $p < 0.05$ was considered statistically significant.

A nomogram based on statistically significant variables from the final multivariable model was constructed. The

Figure 2. Characteristics of different subtypes in older patients with NSAbs-mediated encephalitis. (A) Distribution of antibody subtypes; (B) seizure types in different antibody subtypes, several patients have multiple subtypes of seizures. NMDAR, N-methyl-D-aspartate receptor; LGI1, leucine-rich glioma-inactivated 1; GABAB, γ-aminobutyric acid type B; CASPR2, contactin-associated protein-2.

predictive performance of the nomogram was evaluated as follows: (1) The receiver operating curve (ROC) analysis was used and the area under the curve (AUC) was calculated to evaluate the discrimination of nomogram model, AUC is equal to the C-statistic for the binary model. In addition, ROC-AUC was also applied to compare the predictive performance between prior scoring systems and our nomogram model, the optimal cut-off values were determined by maximizing the Youden index, the optimal sensitivity and specificity were assessed according to the cut-off values; (2) To assess calibration and agreement of nomogram model, the bootstraps of 1000 re-samples were generated and the calibration curves were performed. In addition, the Hosmer–Lemeshow test was carried out for goodness of fit; (3) The decision curve analysis (DCA) was created to evaluate clinical usefulness by measuring the net benefits of the model at different threshold probabilities; (4) the clinical practicability of

the nomogram was also determined by clinical impact curve (CIC). Finally, the internal validation of the nomogram was carried out using the bootstrap method, and a bias-corrected AUC was computed to reflect the predictive performance of model by bootstrap resampling (bootstrap with 1000 repetitions) for validation.

Results

Patient characteristics

Between 01 Jan 2015, and 31 Dec 2021, a total of 147 patients met the inclusion and exclusion criteria based on study design in the final cohort (Fig. 1). Baseline clinical characteristics of included older patients with new-onset seizures of unknown etiology are shown in Table 1. Sixty-eight of 147 participants (46.3%) were diagnosed as NSAbs-mediated encephalitis after antibody detections.

Table 2. Multivariable model for predicting the NSAbs-mediated encephalitis in the elderly with new-onset and symptomatic seizures of unknown etiology.

Variables	Regression coefficient	OR (95% CI)	*p* values
Duration of seizures less than 3 months	2.657	14.259 (4.480–45.386)	<0.001
Seizure types			
Focal-onset	2.522	12.457 (2.710–57.261)	0.001
Generalized-onset	0.458	1.581 (0.240–10.425)	0.634
Unknown		Reference	
Psychiatric deficits	2.309	10.063 (3.231–31.343)	< 0.001
Sleep disorders	1.129	3.091 (1.011–9.454)	0.048
Hyponatremia	1.833	6.252 (1.445–27.043)	0.014
MTL lesions on MRI	1.411	4.102 (1.382–12.169)	0.011
Constant	−5.353	0.005	<0.001

Abbreviations: NSAbs, neuronal surface antibodies, OR, odds ratio; CI, confidence interval; MTL, medial temporal lobe; MRI, magnetic resonance imaging.

In forward-stepwise logistic regression models, the following variables did not include into the final model: seizure frequency ($p = 0.784$), seizure only ($p = 0.974$), cognitive impairment ($p = 0.762$), autonomic dysfunction ($p = 0.356$), pleocytosis in cerebrospinal fluid ($p = 0.090$), positive oligoclonal bands in cerebrospinal fluid ($p = 0.100$).

Of these, the specific antibodies were further classified in Figure 2A. Additionally, the details of seizure types in all NSAbs-positive patients are provided in Figure 2B. Focal-onset seizures were more frequently seen in LGI1 antibodies, and it rarely presented with status epilepticus. While generalized-onset seizures were highly observed in GABAB antibodies. In addition, anti-NMDAR encephalitis is more commonly presented with status epilepticus than other types of antibodies.

Compared with the NSAbs-negative group, patients with NSAbs demonstrated a higher proportion of duration of seizures less than 3 months, seizure types, seizure frequency (daily seizures), seizure only, cognitive impairment, psychiatric deficits, sleep disorders, autonomic dysfunction, pleocytosis in CSF, positive oligoclonal bands in CSF, hyponatremia, and MTL lesions on MRI ($p < 0.05$ for all). No statistically significance was illustrated in other clinical factors, the detailed comparison of patients with and without NSAbs is also given in Table 1.

Independent risk factors of NSAbs-mediated encephalitis on multivariable analysis

The results of multivariable logistic regression analysis using a forward-stepwise method are shown in Table 2. Duration of seizures less than 3 months (OR: 14.259; 95% CI: 4.480–45.386; $p < 0.001$), focal-onset seizures

(OR: 12.457; 95% CI: 2.710–57.261; $p = 0.001$), psychiatric deficits (OR: 10.063; 95% CI: 3.231–31.343; $p < 0.001$), sleep disorders (OR: 3.091; 95% CI: 1.011–9.454; $p = 0.048$), hyponatremia (OR: 6.252; 95% CI: 1.445–27.043; $p = 0.014$), MTL lesions on MRI (OR: 4.102; 95% CI: 1.382–12.169; $p = 0.011$) were independently associated with NSAbs-mediated encephalitis in the elderly with new-onset and symptomatic seizures of unknown etiology after multivariable adjustment.

Development and validation of a nomogram model based on independent risk factors

According to the final multivariable logistic regression analysis, a nomogram model was further constructed to predict the risk probability of the NSAbs-mediated encephalitis in each patient from this cohort (Fig. 3). The nomogram model had a good discrimination with an AUC value of 0.916 (95% CI: 0.872–0.960, Fig. 4A). After the internal validation (bootstrap validation with 1000 repetitions), the nomogram model remained the high discrimination with a bias-corrected AUC value of 0.881. In addition, the calibration curve showed that the predicted result of the nomogram model was in good agreement with the actual observed result (the mean absolute error was 0.041 after 1000 bootstrap repetitions, Fig. 4B). Moreover, the nomogram also performed well on goodness of fit (Hosmer–Lemeshow test, $\chi^2 = 3.559$, $p = 0.895$).

To further assess the clinical usefulness of the nomogram model, the decision curve analysis and clinical impact curve were conducted, and which revealed the nomogram model had a good clinical utility. The decision curve analysis demonstrated that the nomogram model obtained a larger net benefit than "All" or "None" scheme across a reasonable range of the threshold probability (Fig. 4C). Furthermore, the clinical impact curve indicated that the predictive number of patients was nearly consistent with the actual number of true-positive patients when the high-risk threshold was greater than 0.65 (Fig. 4D).

Comparison between current nomogram model and prior scoring systems

In order to highlight the predictive performance of our nomogram model, the comparison between existing scoring systems and our model was further conducted. As shown in Figure 5, our nomogram model showed a better discriminative performance (AUC values) than other existing scoring systems (Our model vs. APE: 0.916 vs. 0.721, $p < 0.001$; Our model vs. APE[2]: 0.916 vs. 0.815, $p = 0.006$; Our model vs. APE[2]-CHN: 0.916 vs. 0.822,
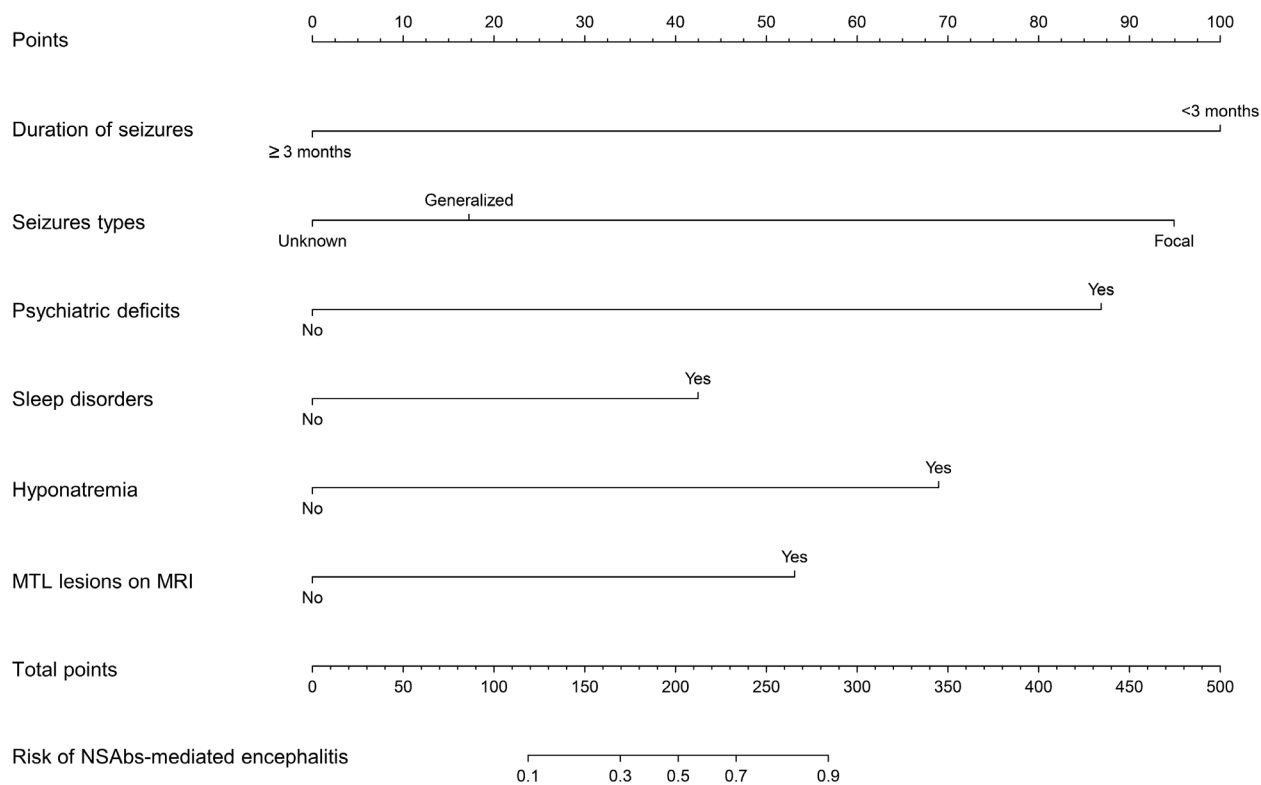
Figure 3. Nomogram for predicting the risk of NSAbs-mediated encephalitis in the elderly with new-onset and symptomatic seizures of unknown etiology. The application is as follows: First, the position of each variable is found on the corresponding axis, a line is then drawn to the Points axis to obtain the number of points for every selected variable. Subsequently, the numbers of points from all six variables are summed, which refers to the total points. Based on the total points, another line is drawn from the Total point's axis to determine risk probabilities of NSAbs-mediated encephalitis at the lower line of the nomogram. MTL, medial temporal lobe; MRI, magnetic resonance imaging; NSAbs, neuronal surface antibodies.

$p = 0.007$). The sensitivity and specificity were respectively presented as follows: 75% and 65.8% for APE; 85.3% and 65.8% for APE^2; 70.6% and 83.5% for APE^2-CHN; 91.2% and 79.7% for our nomogram model.

Discussion

This study suggested that duration of seizures less than 3 months, focal-onset seizures, psychiatric deficits, sleep disorders, hyponatremia, and MTL lesions on MRI were independently associated with the presence of the NSAbs-mediated encephalitis in older patients with new-onset and symptomatic seizures of unknown etiology. Based on these factors, we further developed and validated a nomogram for identifying the odds of NSAbs-mediated encephalitis in individuals, which had a good discriminatory ability (AUC = 0.916) and well-fitted calibration (mean absolute error = 0.041). Additionally, DCA and CIC also demonstrated a higher clinical practicability and better clinical impact for our nomogram model. Finally, our nomogram model showed a greater predictive performance compared with existing scoring systems for new-onset seizures of unknown etiology in the older population.

A deeper understanding of etiology of new-onset seizures or epilepsy in the elderly population is of importance. It is well known that the stroke and Alzheimer's disease are the most common etiologies of new-onset and symptomatic seizures in the elderly.[1] But recently, several studies have suggested that the etiological spectrum is obviously changing over time and revealed autoimmune encephalitis is gradually recognized in the elderly with new-onset seizures or epilepsy.[25] The present study indicated that the NSAbs was observed in 46.3% of the older patients with new-onset seizures of unknown etiology, which was higher than the positive rates of neuronal antibodies previously reported in adult patients (10.5–31.5%).[22,26] On the one hand, the high positive rates might be due to the higher incidence of new-onset seizures in older population as compared with younger adults. On the other hand, the prior study purely relied on serological data without obtaining CSF data, which
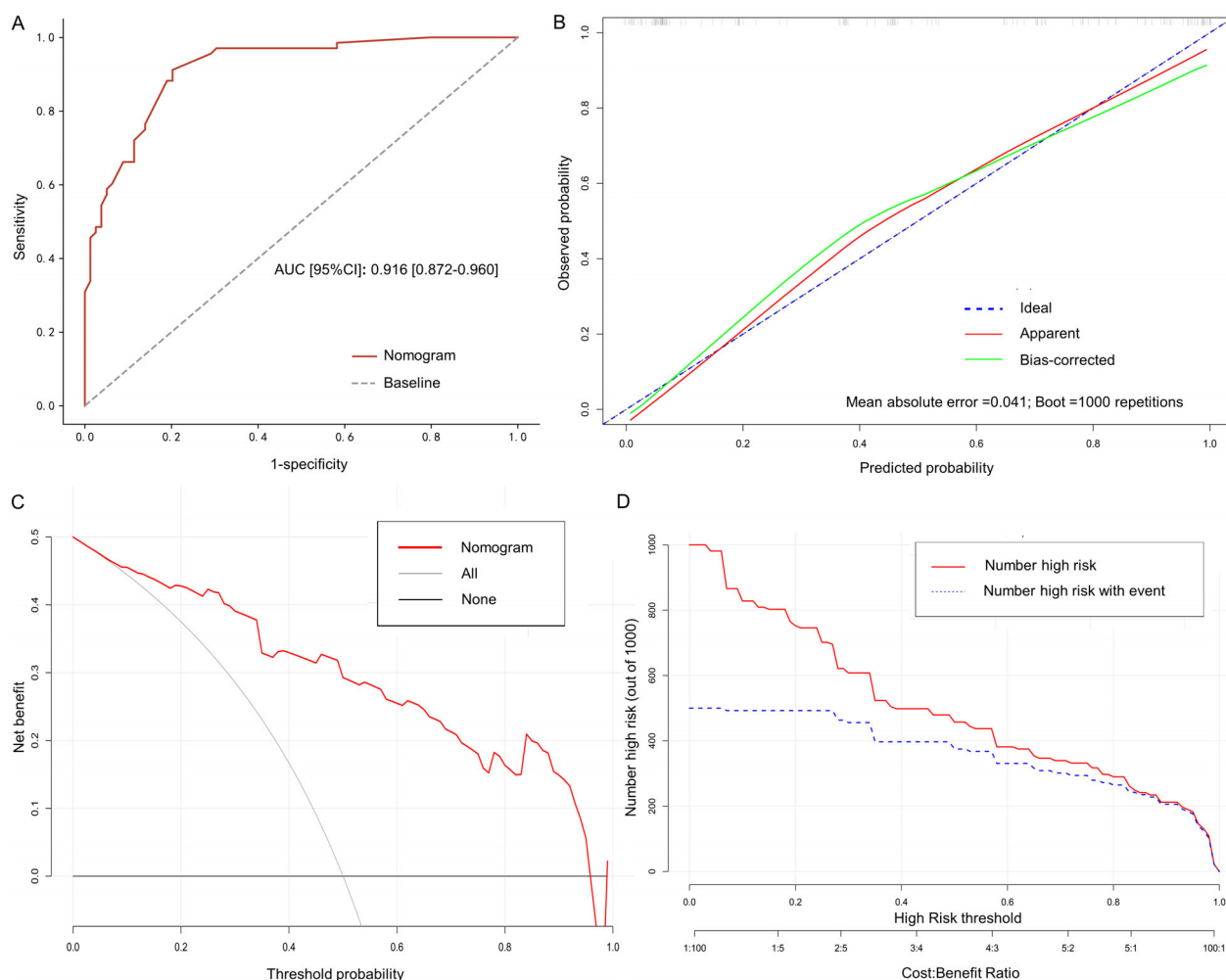
Figure 4. Model performance and validation of the nomogram. (A) ROC for the discrimination of the nomogram. (B) Calibration curve for the nomogram. The calibration plots with bootstrap resampling (boot = 1000 repetitions) show the apparent (actual), bias-corrected (adjusted), and ideal curves and illustrate the good agreement between actual and predicted probability of the nomogram. (C) DCA of the nomogram. The DCA of the nomogram obtains a great net benefit than "All" or "None" scheme across a reasonable range of threshold probability. The threshold probability is plotted on the x-axis, and the net benefit of the nomogram is plotted on the y-axis. (D) CIC of the nomogram. The CIC indicates that the predictive number of patients were nearly consistent with the actual number of true-positive patients when the high-risk threshold was greater than 0.65. The red line (number of patients at high risk) indicates the number of patients who are classified as positive group based on the prediction of the nomogram at each threshold probability, and the blue dotted line (number of patients at high risk with event) is the number of true-positive patients at different threshold probability. AUC, area under the curve; ROC, receiver operating curve; DCA, decision curve analysis; CIC, clinical impact curve.

might lead to the underestimation of antibody-positive rates.[22] In addition, Symonds et al[27] reported that neuronal antibodies were only seen in approximately 6% of children with new-onset epilepsy, which was evidently lower than the older population. Therefore, the detection of neuronal autoantibodies is necessary for older adults with new-onset and symptomatic seizures, particularly in those patients with an unknown etiology.

Although several predictive models have been developed for the diagnosis of antibody-mediated encephalitis in patients with new-onset epilepsy of unknown etiology, there are still no exact standards for diagnosing ASS or AAE. In 2017, the predictive model called APE score was first developed for diagnosis of autoimmune epilepsy.[17,19] Subsequently, the modified Antibody Prevalence in Epilepsy and Encephalopathy (APE^2) score was proposed in 2018, which mainly emphasized the cognitive dysfunction.[18] Recently, APE^2-CHN score has been constructed to focus on predicting the neuronal antibodies for Chinese people.[20] However, our study developed and

Figure 5. Comparison of predictive performance between the nomogram and existing scoring systems. ROC-AUC analysis showed that our model had a better discriminative performance than other existing scoring systems (Our model vs. APE: 0.916 vs. 0.721, *p* < 0.001; Our model vs. APE[2]: 0.916 vs. 0.815, *p* = 0.006; Our model vs. APE[2]-CHN: 0.916 vs. 0.822, *p* = 0.007). ROC, receiver operating curve; AUC, area under the curve; APE, antibody prevalence in epilepsy; CHN, China.
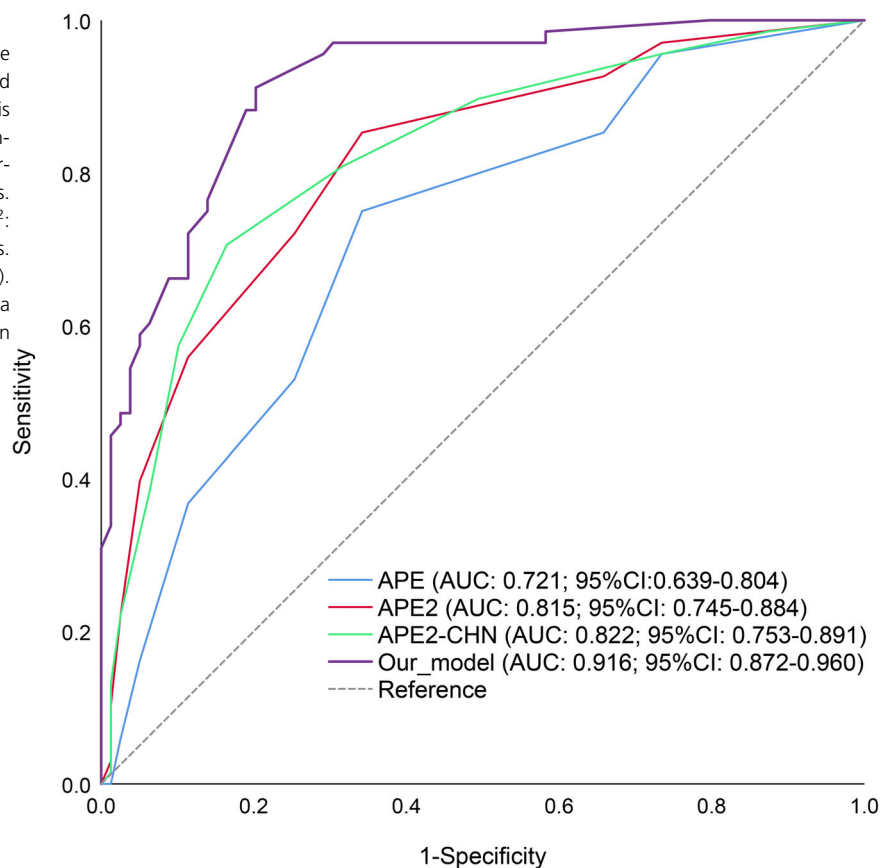
internally validated a novel model for predicting NSAbs in patients with new-onset seizures of unknown etiology. Although our nomogram partly overlapped in some items compared with existing scoring systems (APE/APE[2]/APE[2]-CHN), there are important differences. One of the biggest differences is the study populations, our model focuses on the elderly. Subsequently, ROC-AUC analysis exhibited a better predictive performance compared with APE/APE[2]/APE[2]-CHN, suggesting that our model was more accurate for the elderly population. However, our model still needs more external data for evaluation and validation in the future. In addition, we demonstrated that focal-onset seizures, sleep disorders, and hyponatremia were also associated with the presence of NSAbs in the elderly with new-onset seizures of unknown etiology.

Although there was no report on the association between focal-onset seizures and NSAbs in the elderly with new-onset seizures of unknown etiology, several research have shown that most old-onset seizures were focal in origin, and conversely, most of autoimmune encephalitis also presented with focal-onset seizures or epilepsy,[1,3,28] which may be related to overexpression of antibodies in the hippocampus. FBDS is the unique one of focal-onset seizures in patients with anti-LGI1

encephalitis, which is the most common antibody subtypes for the old population.[8,29] However, the nature of FBDS remains unclear, and further study is needed.

Our study showed that sleep disorders were also associated with the presence of NSAbs in the elderly with new-onset seizures of unknown etiology. Prior studies have reported that sleep disorders are considerable condition in autoimmune encephalitis, because which could interfere patients' recovery and quality of life.[30,31] The potential mechanism may be related to the involvement of middle-line structures in brain, including hippocampus, basal ganglia, thalamus, and hypothalamus.[32] Future research should assess whether optimizing sleep disorders may improve prognosis of seizures. In addition, hyponatremia is specific symptom of anti-LGI1 encephalitis, the prevalence has been reported in approximately 53%–65% of patients.[33,34] Another explanation could be that anti-LGI1 encephalitis is the most common type in the elderly. Thus, the identification of hyponatremia may contribute to determine the risk probability of autoimmune etiology prior to antibody detection in the elderly with new-onset seizures of unknown etiology. But the potential mechanism between hyponatremia and old-onset seizures needs further studies.

Our study has several limitations. (1) The cross-sectional and retrospective nature of current study could not determine other potential risk factors associated with NSAbs in the elderly with new-onset and symptomatic seizures or epilepsy of unknown etiology, such as ^{18}F-fluorodeoxy-glucose positron emission tomography (^{18}F-FDG-PET). Prior studies have shown that ^{18}F-FDG-PET may play a key role in the diagnosis of autoimmune encephalitis,[35] but these imaging data were not available for all included patients in this retrospective study. Additionally, we did not cover the entire repertoire testing for NSAbs, such as novel DPPX, IgLON5, which may lead to underestimation of positive NSAbs and our nomogram may be corrected in the future with recognition of novel NSAbs. Finally, it is worth noting that a substantial proportion of patients were excluded due to lack of antibody testing or baseline information, which may imply selection bias. (2) We could not systematically investigate the relevant risk factors in the specific antibody subtypes due to a relatively small sample size. However, regardless of antibody types, the immunosuppression is the first-line treatment for definite NSAbs-mediated encephalitis and the current limitations may serve as the potential avenues for future studies. (3) Our nomogram model was developed and internally validated according to our single-center data, and future research regarding the model performance of our nomogram should be further externally validated in prospective cohorts from other centers.

In summary, autoimmune encephalitis associated with NSAbs is an increasingly noteworthy etiology of new-onset seizures with unknown etiology in the elderly. Our nomogram model combining these clinical factors provide a useful tool for the presence of NSAbs in the elderly with new-onset and symptomatic seizures of unknown etiology. Identifying and improving these risk factors may help inform early immunologic intervention therapy and further reduce the probability of developing the chronic epilepsy. A multicenter and prospective cohort should be conduct to correct and validate these results in the future.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by XL, TY, JQ, and RL. The first draft of the manuscript was written by XL and QW. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

Ethical Approval and Consent to Participate

This study was conducted in accordance with principles of the Declaration of Helsinki. Ethics approval was obtained from the Ethics committee of the Beijing Tiantan hospital, Capital Medical University. All patients provided informed consent for the use of their medical records.

Data availability statement

All data relevant to the study are either included in the article or shared at the request of any qualified investigator.

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